CBER Update: Advertising and Promotional Labeling Branch (APLB)

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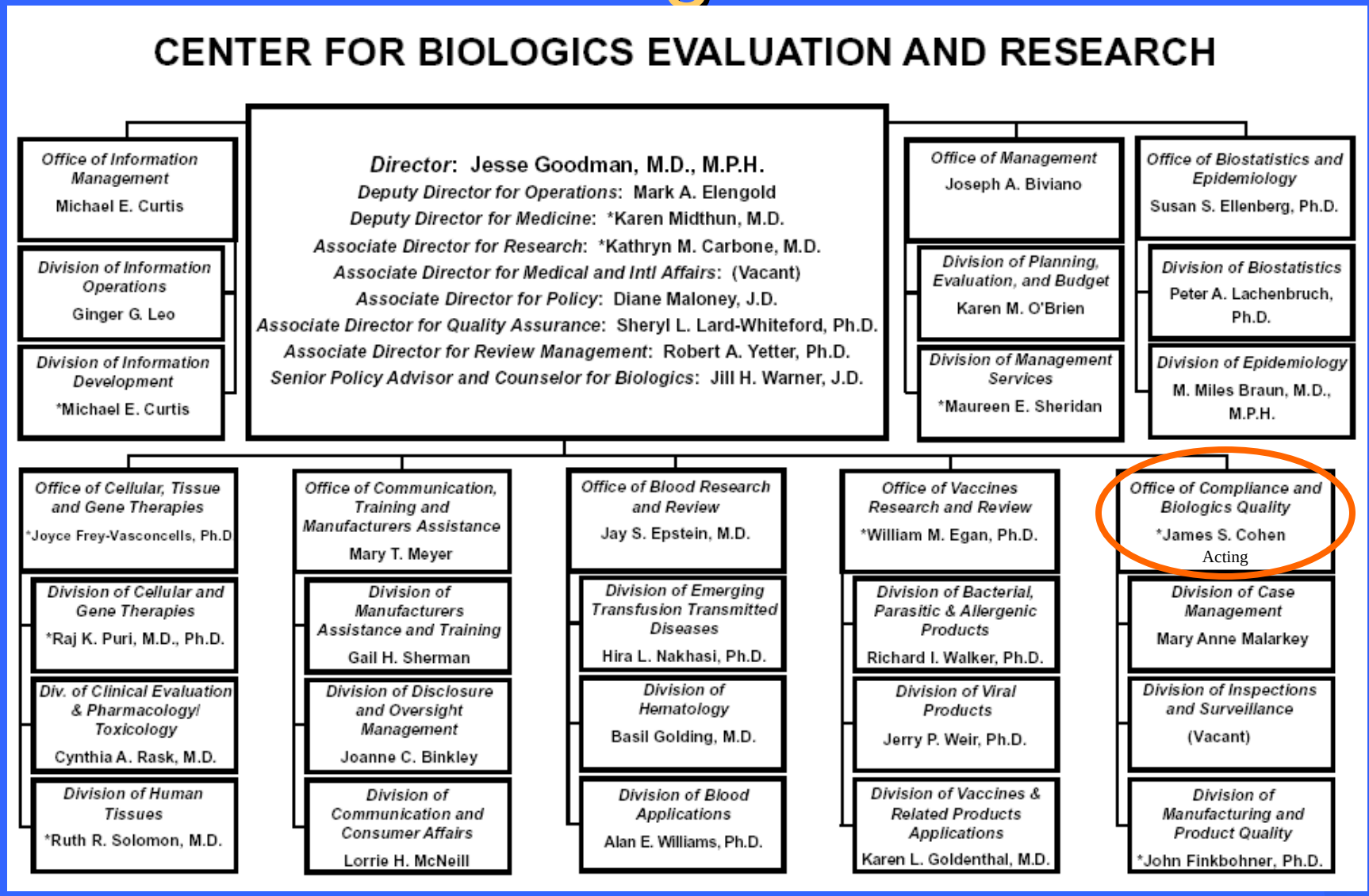
Division of Case Management
Office of Compliance and Biologics Quality

FDLI Conference: Advertising and Promotion for the Pharmaceutical, Veterinary Medicine, Biologics, and Medical Device Industries
September 13-14, 2004

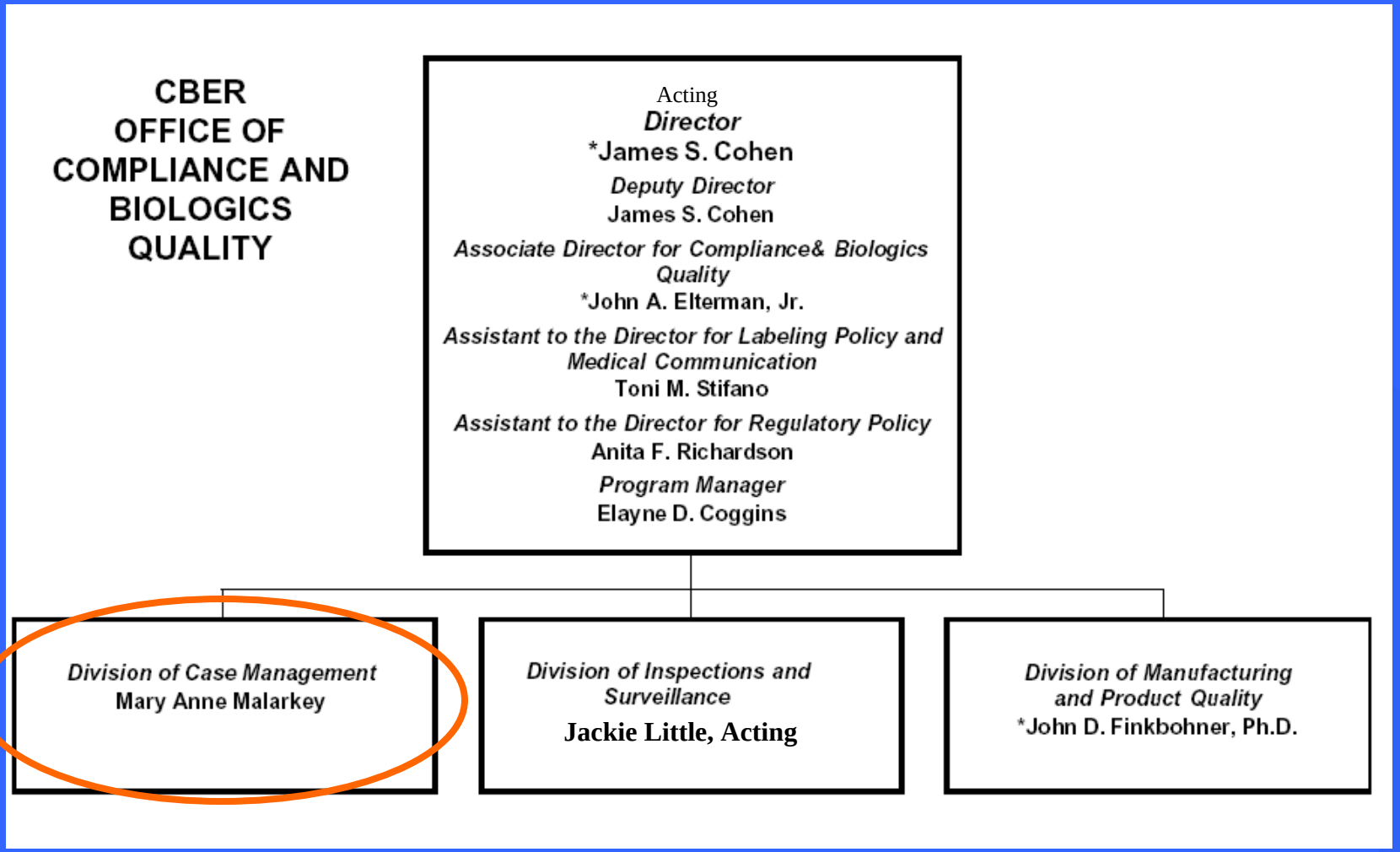
Agenda

- Update on APLB
- Enforcement Actions and Examples
- APLB Priorities

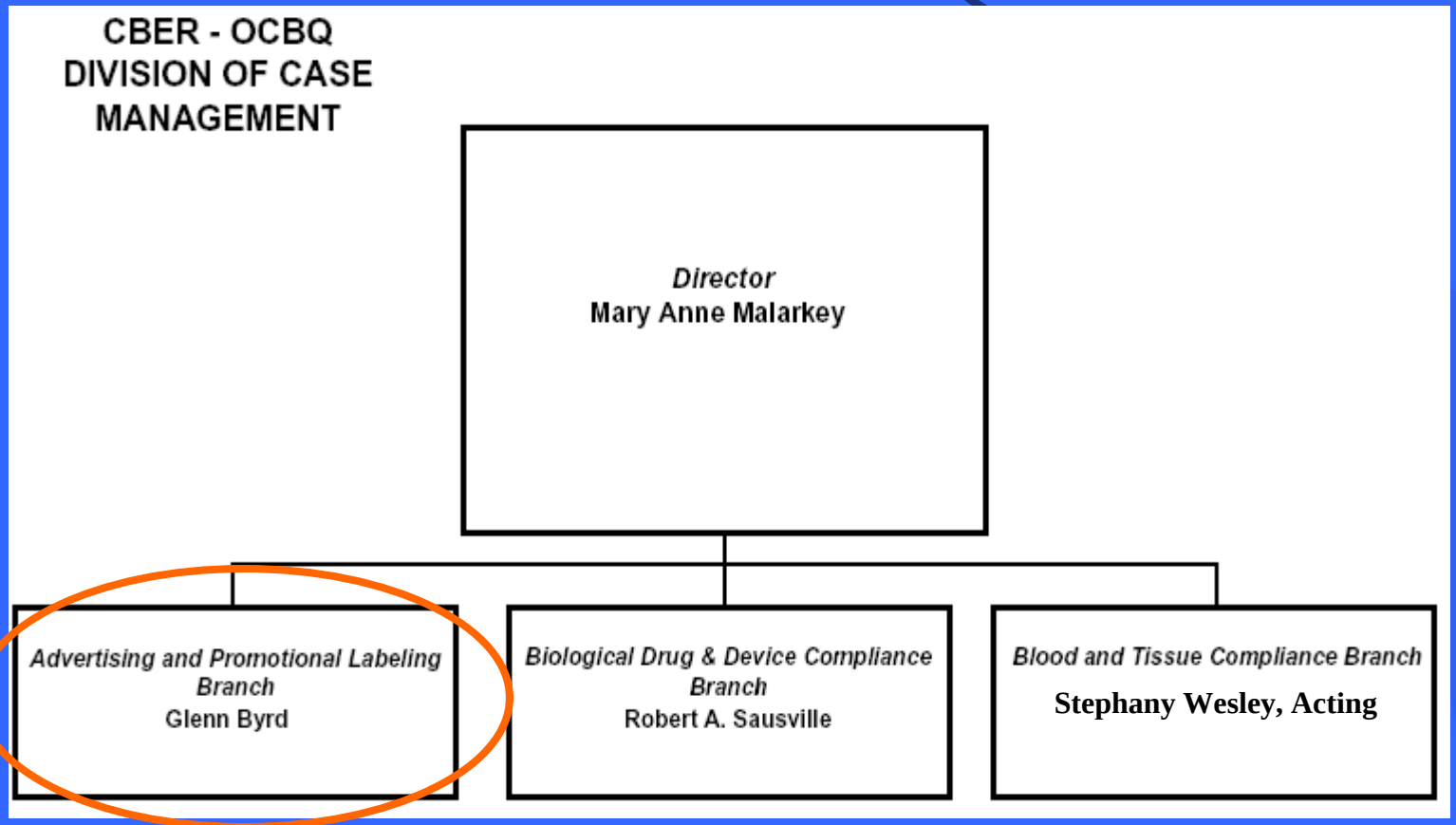
CBER Organization



CBER/APLB Organization



CBER/APLB Organization



APLB Staff

- Glenn Byrd, MBA, RAC - Chief
- Nancy Chamberlin, Pharm.D.
- Maryann Gallagher
- Yongkai Weng, Ph.D.
- Open staff position

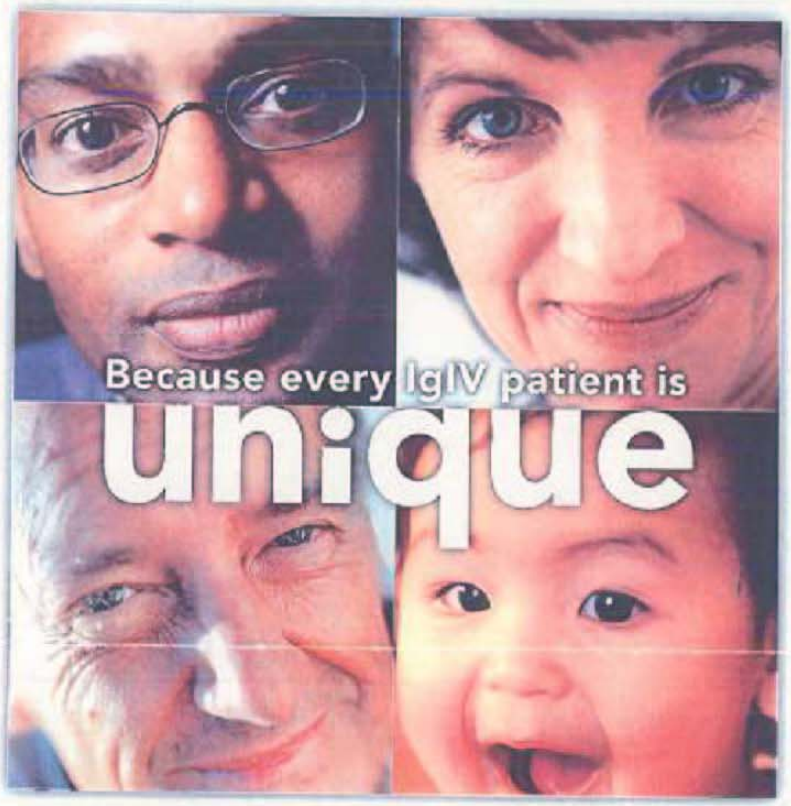
APLB Enforcement FY-04

- Untitled Letters – seven (7) issued
  - Comvax – Merck (12/03)
  - Theracys – Aventis Pasteur (1/04)
  - ReFacto – Wyeth Pharmaceuticals (2/04)
  - Imogam/Imovax – Aventis Pasteur (2/04)
  - Typhim Vi – Aventis Pasteur (4/04)
  - Vivotif – Berna Biotech (6/04)
  - Helixate FS – Bayer HealthCare (8/04)

APLB Enforcement FY-04

- Warning Letters – five (5) issued since May '04
  - Polygam S/D - Baxter Healthcare (5/04)
  - Advate - Baxter Healthcare (5/04)
  - Crosseal - Omrix biopharmaceuticals (5/04)
  - Engerix-B, Havrix, Twinrix – GlaxoSmithKline Biologics (7/04)
  - NovoSeven – Novo Nordisk Pharmaceuticals (8/04)

- All CBER Enforcement letters are posted at: www.fda.gov/cber/efoi/adpromo.htm



No two people in the world are exactly the same. Many patients with compromised immune systems are unique, too, and POLYGAM® S/D is the IgIV therapy that can help meet their varied needs.

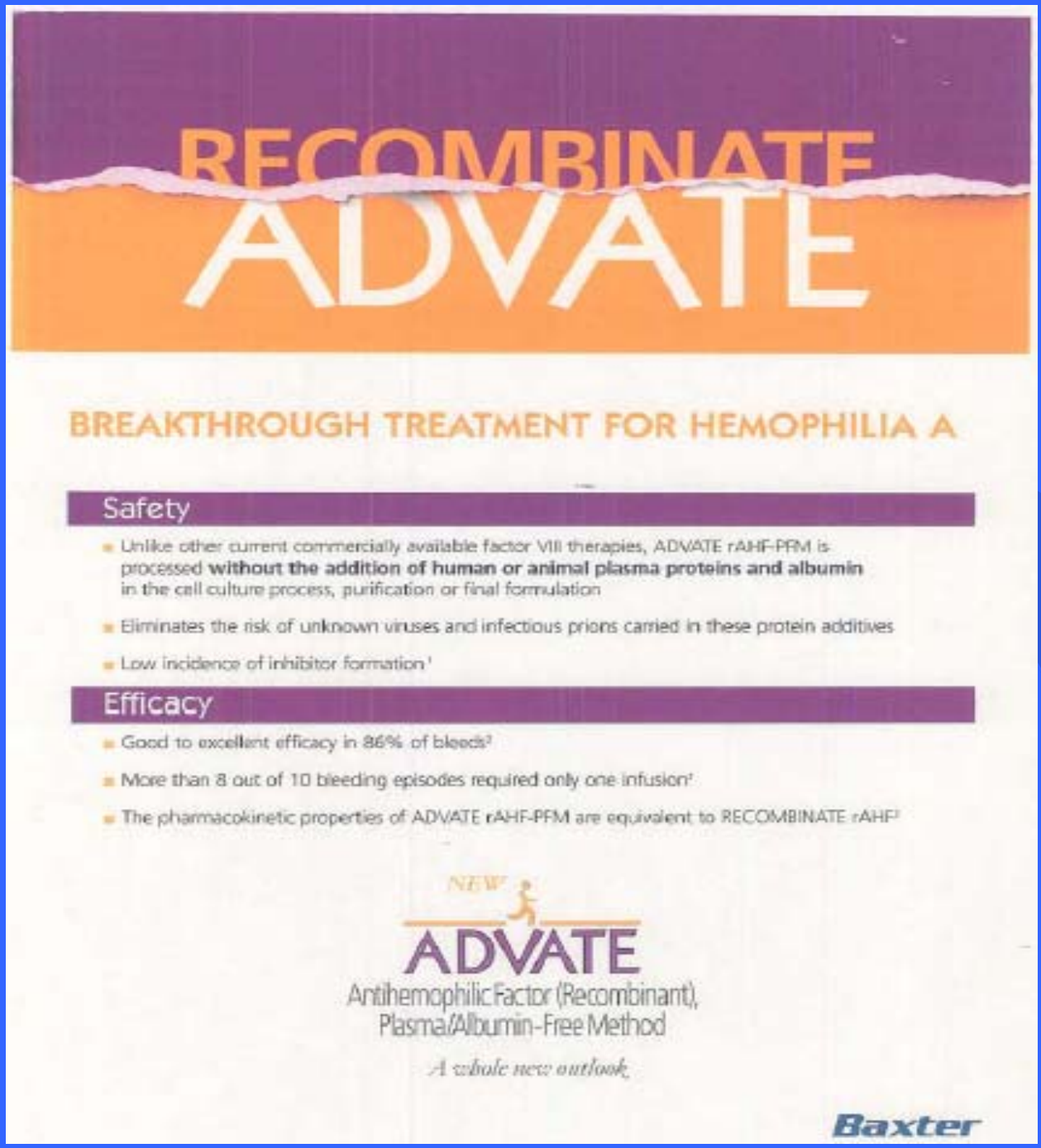
At ≤1.2 µg IgA/mL, POLYGAM® S/D 5% solution has one of the lowest IgA content levels of any IgIV product to accommodate patients with antibodies to IgA or selective IgA deficiencies.* POLYGAM® S/D is ideal for those patients for whom a sucrose-free formula is preferred.

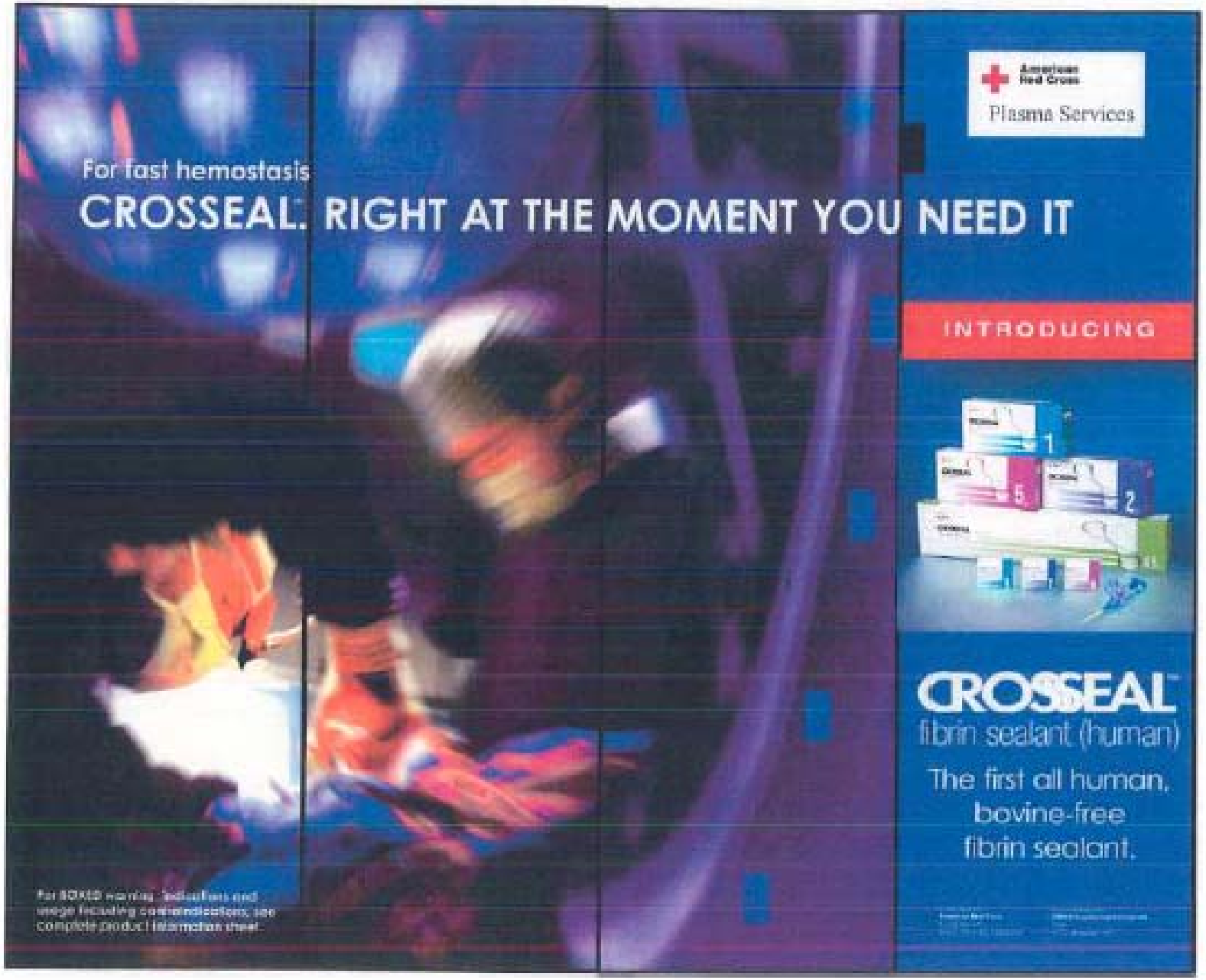
And to meet the safety needs of all IgIV patients, POLYGAM® S/D uses a solvent detergent treatment to inactivate lipid-enveloped viruses.

Every IgIV patient is unique, but with POLYGAM® S/D they can all share the long-standing commitment of the American Red Cross to meet their individual needs.

Polygam® S/D
Immune Globulin Intravenous (Human)
SOLVENT/DETERGENT TREATED

Manufactured for:
American Red Cross
Plasma Services


RECOMBINATE
ADVATE
BREAKTHROUGH TREATMENT FOR HEMOPHILIA A
Safety
Unlike other current commercially available factor VIII therapies, ADVATE rAHF-PFM is processed without the addition of human or animal plasma proteins and albumin in the cell culture process, purification or final formulation
Eliminates the risk of unknown viruses and infectious prions carried in these protein additives
Low incidence of inhibitor formation[1]
Efficacy
Good to excellent efficacy in 86% of bleeds[2]
More than 8 out of 10 bleeding episodes required only one infusion[2]
The pharmacokinetic properties of ADVATE rAHF-PFM are equivalent to RECOMBINATE rAHF[2]
NEW
ADVATE
Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method
A whole new outlook
Baxter


For fast hemostasis
CROSSEAL: RIGHT AT THE MOMENT YOU NEED IT
American Red Cross
Plasma Services
INTRODUCING
CROSSEAL
fibrin sealant (human)
The first all human, bovine-free fibrin sealant.

Summary of Recommendations for Adult Immunization

Adapted from: Advisory Committee on Immunization Practices (ACIP) and Immunization Action Coalition (Item #P2011) Vaccine

NAME AND ROUTE	For whom it is recommended	Schedule for routine and "catch-up" administration	Contraindications (mild illness is not a contraindication)
Influenza Inactivated influenza vaccine (IIV) *Give IM* Live attenuated influenza vaccine (LAIV) *Give intranasally*	• All adults who are 50yrs of age or older. • People 6m–50yrs of age with medical problems (e.g., heart disease, lung disease, diabetes, renal dysfunction, hemoglobinopathies, immunosuppression) and/or people living in chronic care facilities. • People (>6m of age) working or living with at-risk people. • Pregnant women who have underlying medical conditions should be vaccinated before influenza season, regardless of the stage of pregnancy. • Healthy pregnant women who will be in their 2nd or 3rd trimesters during influenza season. • All healthcare workers and those who provide essential community services. • Travelers who go to areas where influenza activity exists or who may be among people from areas of the world where there is current influenza activity (e.g., on organized tours). • Anyone wishing to reduce the likelihood of becoming ill with influenza.	• Given every year. • October through November is the optimal time to receive an annual flu shot to maximize protection. • Influenza vaccine may be given at any time during the influenza season (typically December through March) or at other times when the risk of influenza exists.	• Previous anaphylactic reaction to this vaccine, to any of its components, or to eggs. • Moderate or severe acute illness. • Do not give live attenuated influenza vaccine (LAIV) to persons >50 years of age, pregnant women, or to persons who have: asthma, reactive airway disease or other chronic disorder of the pulmonary or cardiovascular systems; an underlying medical condition, including metabolic diseases such as diabetes, renal dysfunction, and hemoglobinopathies; a known or suspected immune deficiency disease or who are receiving immunosuppressive therapy; a history of Guillain-Barré syndrome. **Note:** Use of inactivated influenza vaccine (IIV) is preferred for persons in close contact with immunosuppressed persons.
Pneumococcal polysaccharide (PPV23) *Give IM or SC*	• Adults who are 65yrs of age or older. • People 2–64yrs of age who have chronic illness or other risk factors, including chronic cardiac or pulmonary diseases, chronic liver disease, alcoholism, diabetes mellitus, CSF leaks, candidate for or recipient of cochlear implant, as well as people living in special environments or social settings (including Alaska Natives and certain American Indian populations). Those at highest risk of fatal pneumococcal infection are people with anatomic asplenia, functional asplenia, or sickle cell disease; immunocompromised persons including those with HIV infection, leukemia, lymphoma, Hodgkin's disease, multiple myeloma, generalized malignancy, chronic renal failure, or nephrotic syndrome; persons receiving immunosuppressive chemotherapy (including corticosteroids); and those who received an organ or bone marrow transplant. Pregnant women with high-risk conditions should be vaccinated if not done previously.	• Routinely given as a one-time dose; administer if previous vaccination history is unknown. • One-time revaccination is recommended 5yrs later for people at highest risk of fatal pneumococcal infection or rapid antibody loss (e. g., renal disease) and for people >65yrs of age if the 1st dose was given prior to age 65 and >5yrs have elapsed since previous dose.	• Previous anaphylactic reaction to this vaccine or to any of its components. • Moderate or severe acute illness. **Note:** Pregnancy and breastfeeding are not contraindications to the use of this vaccine.
Hepatitis B (Hep B) *Give IM*	• All adolescents. • High-risk adults, including household contacts and sex partners of HBsAg-positive persons; users of illicit injectable drugs; heterosexuals with more than one sex partner in 6 months; men who have sex with men; people with recently diagnosed STDs; prostitutes; patients receiving hemodialysis and patients with renal disease that may result in dialysis; recipients of certain blood products; healthcare workers and public safety workers who are exposed to blood; clients and staff of institutions for the developmentally disabled; inmates of long-term correctional facilities; and certain international travelers. **Note:** Prior serologic testing may be recommended depending on the specific level of risk and/or likelihood of previous exposure. Note: In 1997, the NIH Consensus Development Conference, a panel of national experts, recommended that hepatitis B vaccination be given to all anti-HCV positive persons. **Ed. note:** Provide serologic screening for immigrants from endemic areas. When HBsAg-positive persons are identified, offer appropriate disease management. In addition, screen their sex partners and household members and, if found susceptible, vaccinate.	• Three doses are needed on a 0, 1, 6m schedule. • See full prescribing information for alternate schedules and dosing in special populations,such as dialysis patients.	• Previous anaphylactic reaction to this vaccine or to any of its components. • Moderate or severe acute illness. **Note:** Pregnancy Category C. This vaccine should be given to a pregnant woman only when clearly needed. Caution should be exercised when administering hepatitis B vaccination to a nursing woman.
Hepatitis A (Hep A) *Give IM*	• People who travel outside of the U.S. (except for Western Europe, New Zealand, Australia, Canada, and Japan). • People with chronic liver disease, including people with hepatitis C; people with hepatitis B who have chronic liver disease; illicit drug users; men who have sex with men; people with clotting-factor disorders; people who work with hepatitis A virus in experimental lab settings (not routine medical laboratories); and food handlers when health authorities or private employers determine vaccination to be cost effective. **Note:** Prevaccination testing is likely to be cost effective for persons >40yrs of age as well as for younger persons in certain groups with a high prevalence of hepatitis A virus infection.	For Twinrix® [Hepatitis A Inactivated & Hepatitis B (Recombinant) Vaccine] three doses are needed on a 0, 1, 6m schedule. • Two doses are needed. • The minimum interval between dose #1 and #2 is 6m. • If dose #2 is delayed, do not repeat dose #1. Just give dose #2	• Previous anaphylactic reaction to this vaccine or to any of its components. • Moderate or severe acute illness. • Safety during pregnancy has not been determined, so benefits must be weighed against potential risk. **Note:**Pregnancy Category C. This vaccine should be given to a pregnant woman only when clearly needed. Caution should be exercised when administering hepatitis B vaccination to a nursing woman.

Things your hematologist will consider when planning treatment

The type of inhibitor you have will make a difference in your treatment. If you have a low-responding inhibitor, you may continue receiving the same treatment as before the inhibitor developed. Or, you may need more than the usual amount of factor VIII or factor IX to override the inhibitor and control your bleeding.[1]

If you have a high-responding inhibitor, your treatment will likely be more complicated. Your bleeding may be treated with a **bypassing product**, or a therapy called **immune tolerance therapy (ITT)** may be used to get rid of the inhibitor.[1]

Bypassing products work with platelets and other clotting factors (skipping some of the normal steps where factor VIII and factor IX are needed) to make a blood clot and stop the bleeding, even when there isn't enough factor VIII or factor IX in your blood.[1]

Because every person with inhibitors is different, it is important to talk with your HTC staff about the possible treatments that are right for you.

What bypassing agents are available?

There are several different types of treatments that your HTC staff may discuss with you:

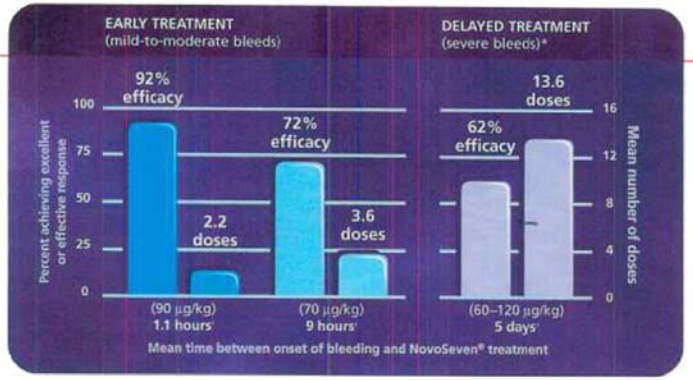
- NovoSeven® (Recombinant factor VIIa)[1]
  - — Contains activated factor VII, one of the clotting factors in plasma
  - — Can be used with all types of inhibitors
  - — Is made from **recombinant technology** that does not use human plasma
  - — Does not contain factor VIII or factor IX, so the inhibitor is less likely to keep rising
- Prothrombin complex concentrates (PCCs)[1]
  - — Are made from human blood products
  - — Contain factor II (two), factor VII (seven), factor IX (nine), and factor X (ten)
- Activated prothrombin complex concentrates (APCCs)[1]
  - — Are made from human blood products
  - — Contain activated factor II, factor VII, factor IX, and factor X
- Porcine factor VIII
  - — Is made from the blood of pigs[5]
  - — Helps stop bleeding in people with factor VIII inhibitors, because the pig factor VIII is not attacked as often by inhibitors to human factor VIII[3]
  - — May cause a rise in inhibitors to pig and/or human factor[5]
  - — Has a high risk of allergic reactions[3,5]

Talk to your HTC to understand the treatment plan that's been designed just for you

For the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to FVIII or FIX

NovoSeven®:
Clinical advantages with early treatment

3 NovoSeven® studies of treatment for intramuscular bleeds[1-3]



* NovoSeven® used as salvage therapy.

Three separate studies analyzed a total of 245 peripheral intramuscular bleeding episodes. Time from onset of bleed until first treatment, dosage, number of doses, and responses were recorded for each study. Enrolled subjects had hemophilia A or B with inhibitors (several patients in the late treatment study had acquired inhibitors; several patients in the early treatment study [treatment after 9 hours] had hemophilia without inhibitors).

"...data suggest that in >90% of cases... early administration of rFVIIa achieves haemostasis after 1 to 3 injections. In more than 90% of responders, haemostasis is maintained for at least 24 h."[1]

—Key NS et al, 1998

- **Early administration of coagulation factor in patients with bleeding episodes can reduce pain and the risk of arthritis and permanent disability**[4]

novo nordisk®

NovoSeven®
Coagulation Factor VIIa (Recombinant)
Tab 2
The recombinant clamp

Problems from Warning Letters

- Complete omission of risk from the body of the item, including for products with black box warnings
- False or misleading safety claims
  - Claims regarding the reduction in frequency or severity of adverse events or clinical symptoms in the absence of substantial evidence
  - False information on approved indications and limitations of other marketed products
  - Claims of “unsurpassed…safety”

Description of Problems

- Unsubstantiated effectiveness claims
  - Promotion of broader indication than approved
  - Lack of definition of terminology, e.g., “fast hemostasis,” when such terms are directly relevant to the approved indication for use
- Failure to submit advertising and promotional materials to CBER at the time of dissemination

Convention Panels

- Important points to consider when developing/approving convention panels:
  - Fair Balance risk information should be included in the body of the convention panel
  - It is not sufficient to simply post the PI next to the panel.

Corrective Actions

- Warning letters – firms requested to develop a plan of action to distribute corrective information to audience that received violative information
- Examples:
  - Conferences – send letters to all conference attendees
  - Journals – send letters to all subscribers or publish a corrective ad in journal(s)

APLB Priorities

- Fill vacant staff position
- Vigorous enforcement action
- Guidance development
- Work interactively with industry

- APLB Contact Info
  - Phone: 301-827-3028; Fax: 301-827-3528